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HSM-LUP-CP2

4 December 2004

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Authorised officer: Ms. Monica Ferro

No. Of pages: 15

Dear Sirs,

Re: LUPIN LIMITED *et al.*
PCT International Application No. PCT/IN03/00003
Filed on: 6th January 2003

The Hon'ble IPEA had been kind enough to grant us an extension of time until **13 December 2004** to file a response to the written opinion.

We note that the International Search Report has cited three documents in the "Y" category, relevant to claims 1-17 of the above-identified application, which collectively question the inventive step of the invention embodied therein.

The applicants have studied all the three citations and have reasons to believe that the invention embodied in their application is different and not obvious in view of said citations. The distinguishing features of the applicants' invention vis-à-vis that embodied in the three documents cited in the Search Report are given below:

1. *BACKGROUND*

Cefpodoxime proxetil – a process for which the present invention relates to- is an orally administrated semi-synthetic third generation cephalosporin antibiotic having an extended spectrum of activity. Cefpodoxime axetil is the prodrug of the active metabolite, cefpodoxime, which exhibits *in vitro* activity against a wide range of gram-positive and gram-negative bacteria. It also exhibits remarkable stability towards β-lactamase enzymes.

Cefpodoxime proxetil, as shown below is characterized by the presence of a

a. methoxymethyl group at the 3α-position;

b. 2-(2-aminothiazol-4-yl)-2(Z)-methoxyimino-acetamido function at the 7β-position, and

c. 1-[(isopropoxycarbonyl)oxy]ethyl carboxylic acid ester group at the 4-position of the molecule.

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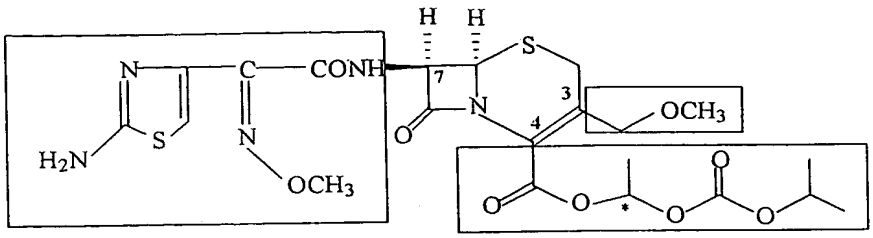


Further, the asymmetric centre at the α-carbon of the 1-[(isopropoxycarbonyl)oxy]ethyl group attached to 4-carboxylic acid function, marked with the asterik (*) exists as a pair of diastereoisomers, notated as the (R) and (S) isomers. Pharmacopoeial Forum Vol : 28 (1), pp 44-52 (2002) specifies that the diastereoisomeric ratio (R/R+S) isomers in cefpodoxime proxetil should be between 0.5 to 0.6.

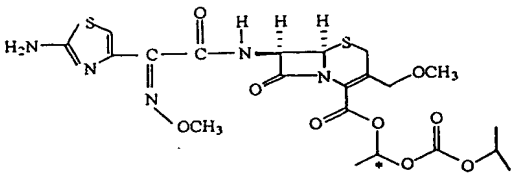
Of the abovementioned three functional groups,

i) 1-[(isopropoxycarbonyl)oxy]ethyl carboxylic acid ester group at the 4-position of the molecule, by virtue of being a carbonate is highly sensitive to basic conditions to undergo hydrolysis,

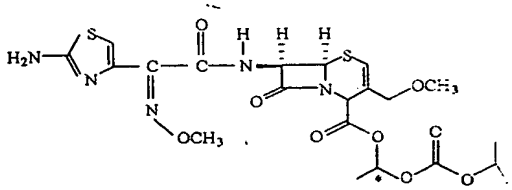
ii) the (R) and (S) isomers of the said 1-[(isopropoxycarbonyl)oxy]ethyl carboxylic acid ester group, by virtue of being diastereoisomers differ in their physical properties, specially solubility. In view of their differential solubility in various solvents, more often than not, in a method of manufacture of cefpodoxime proxetil a product, in which the said disatereoisomeric ratio is disturbed and which, therefore does not conform to the diastereoisomeric ratio of (R/R+S) = 0.5 to 0.6, as specified in pharmacopoeia is obtained, which, further requires additional operations for adjustment of the ratio to the desired level; and

iii) the free amino group at 2-position of the 2-(2-aminothiazol-4-yl)-2(Z)-methoxyimino-acetamido addendum at the 7β-position of the molecule, by virtue of being a reactive function, more often than not, in a method of manufacture of cefpodoxime proxetil is highly prone to undergo reactions that a normal amino function is expected to and thereby, results in side-reactions and formation of undesirable side-products/degradation products, which, in turn renders the product obtained again not conforming to pharmacopoeial specifications with respect to the level of impurities.

In addition, the double bond at 3-position (Δ^3-isomer) of the molecule is highly susceptible to isomerization to the 2-position (Δ^2-isomer) under basic conditions and the Δ^2-isomer once formed is very difficult to remove, again leaving behind a product not conforming to pharmacopoeial specifications as shown below.



The delta-3-isomer of Cefpodoxime proxetil



The delta-2-isomer of Cefpodoxime proxetil

Several improvements have been effected in the prior art to address the above issues, and obtain pure cefpodoxime proxetil having the desired diastereoisomeric ratio, free of impurities specially the Δ^2-isomer either through:

a. protection of the reactive amino group and its subsequent deprotection to minimize/eliminate formation of side-products;

b. improvements in the reaction conditions or selection of reaction parameters to minimize/eliminate the formation of the Δ^2-isomer; or

c. utilization of varied crystallization and isolation methods to obtain cefpodoxime proxetil having the desired diastereoisomeric ratio.

Such methods, however, are associated with several shortcomings, as would be evident from the discussion given in the **BACKGROUND OF THE PRESENT INVENTION** Section of the applicants' Specification i.e., their PCT International Application No. PCT/IN03/00003.

2. ***THE INVENTION RESIDING IN THE APPLICANTS' APPLICATION No. PCT/IN03/00003***

The invention residing in the applicants' PCT International Application No. PCT/IN03/00003 is a step forward in this direction. It provides a simple method for obtaining cefpodoxime proxetil of high purity, substantially free of impurities including the Δ^2-isomer, conforming to pharmacoepial specifications and more importantly having a diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6.

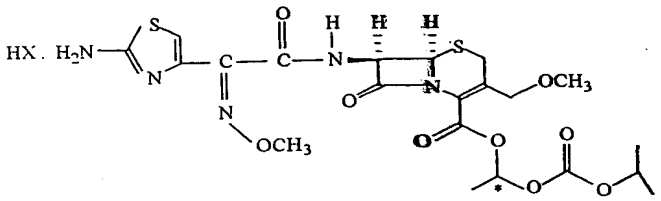
The invention provides a selective method of obtaining cefpodoxime proxetil of high purity and conforming to pharmacoepial specifications, which comprises the steps of :

a) reaction of a solution of impure cefpodoxime proxetil in a water-immiscible organic solvent with a solution of an organic acid in water to form the corresponding acid addition salt of cefpodoxime proxetil;

b) selective partitioning of the acid addition salt of cefpodoxime proxetil thus formed in water and the impurities in the organic phase; and

c) neutralization of the aqueous solution of the acid addition salt of cefpodoxime proxetil to give cefpodoxime proxetil of high purity and conforming to pharmacoepial specifications.

It might be mentioned herein that the acid addition salt is formed at the free amino function attached to 2-position of the 2-amino thiazol-4-yl-methoxyimino acetamido addendum at the 7β-position of the molecule, as shown hereinbelow.



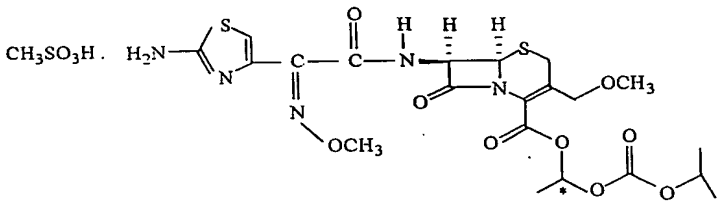
HX = An acid

The acid addition salt of Cefpodoxime proxetil

Thus, in principle the invention takes advantage of the difference in solubility of the acid addition salts of cefpodoxime proxetil and the impurities in water and the water-immiscible organic solvent respectively to achieve the desired purification and thereby meeting the objective of obtaining cefpodoxime proxetil of high purity and conforming to pharmacoepial specifications and more importantly having a diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6.

However, even though the free amino function attached to 2-position of the 2-amino thiazol-4-yl-methoxyimino acetamido addendum at the 7β-position of the molecule is capable of forming the acid addition salt with any organic acid, specially strong acids like hydrochloric, hydrobromic, sulfuric, p-toluenesulfonic, benzenesulfonic, trifluroacetic acid etc. it was found that such salts do not have complete solubility in water. This results in a situation wherein the said salts are partitioned partly in the organic phase along with the impurities and in turn, disturbing the diastereoisomeric ratio of (R/R+S) isomers of cefpodoxime proxetil partitioned in the aqueous phase.

Of all the organic acid addition salts, only the salt of cepfpodoxime proxetil with methanesulfonic as shown below (obtained by reacting a solution of impure cefpodoxime proxetil in a water-immiscible organic solvent with a solution of methanesulfonic acid in water) was found to be highly soluble in water with concomitant partitioning of all the impurities in the organic phase, leaving in the aqueous phase a highly pure methanesulfonic acid salt of cefpodoxime proxetil, substantially free of impurities and more importantly having a diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6.



The Methanesulfonate salt of Cefpodoxime proxetil

Pure cefpodoxime proxetil having the desired diastereoisomeric ratio of (R/R+S) isomers is then obtained by simple neutralization of the methanesulfonate salt in water with a base.

The high selectivity exhibited by methanesulfonic acid over other acids in making the salt obtained thereof highly soluble in water, thereby effecting the most optimum separation of impurities in the organic phase forms the inventive step of the present invention.

3. *ANALYSIS OF THE CHEMISTRY PRACTICED IN THE DOCUMENTS CITED IN THE INTERNATIONAL SEARCH REPORT VIS-À-VIS THAT EMBODIED IN THE APPLICANTS' APPLICATION*

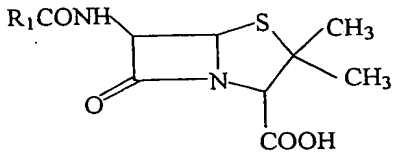
At the outset, it is respectfully submitted that none of the three documents cited in the International Search Report can be found to have any connection with the method of preparation of pure cefpodoxime proxetil, disclosed in the applicants' PCT International Application No. PCT/IN03/00003.

Our comments are based on the analysis of the distinguishing features of the invention residing in the PCT International Application No. PCT/IN03/00003 *vis-à-vis* that disclosed in the abovementioned three documents:

3A. ***Chapter 19, tiled, "Use of Solvent Extraction in Pharmaceutical manufacturing Process", pages 583-591 in the book, "Handbook of Solvent Extraction", Teh C. Lo., Malcolm H.I., and Baird C.H. Ed., John Wiley & Sons (1983).***

This document, marked "Y" by the Hon'ble IPEA and in the present context designated as D1 essentially relates to a method of isolation of pharmaceutical compounds through a solvent extraction process, (which needless to mention, has been practiced since ages in the chemical industry). As mentioned at the outset, D1 has no connection, whatsoever, with the method of preparation of pure cefpodoxime proxetil, disclosed in the PCT International Application No. PCT/IN03/00003.

This document D1, specifically, deals with a method of isolation and purification of antibiotic compounds, more specifically naturally occurring penicillin antibiotics, represented by the general formula shown below, from a fermentation broth in which they are manufactured through a solvent extraction process. The most important of such penicillins are the commercially and therapeutically valuable Penicillin G (R_1 = benzyl) and Penicillin V (R_1 = phenoxymethyl).



The method for extraction and subsequent isolation of penicillins from the fermentation broth in which it is manufactured as described in D1, takes advantage of the preferential solubility exhibited by the said penicillins in organic solvents rather than water, and the preferential solubility exhibited by the salts of the said penicillins in water rather than an organic solvent. The selective distribution ratios of the penicillin and its salts in the organic solvent and water respectively has the advantage of extracting the most optimum quantity of penicillin from the broth while selectively rejecting most of the unwanted impurities.

This document D1, further mentions that the penicillins can also be directly precipitated from the organic solvent by raising the pH of the solution through addition of a concentrated (meaning little water) acetate or phosphate buffer. The raising of the pH results in the formation of the appropriate salt, which is thrown out of the two-phase

mixture of the solvent and the buffer. In addition, D1 mentions that the solution of the penicillin in an organic solvent can also contacted with a dilute buffer (meaning more water). The salt thus formed then passes into the aqueous phase, which on acidification regenerates the free acid and thereby passing it on to the organic phase. The said penicillin in the organic phase is crystallized in pure form through formation of its salts.

From the description in Section 2.2 of D1 it would be evident that the penicillins referred to therein have a free carboxylic acid function at the 3-position of the molecule, by virtue of which they are capable of forming the salts mentioned therein. The salts that are formed are conventional salts specially alkali metal salts such as sodium and potassium or organic base salts (See Section 2.2).

Even though, there is mention in Section 2.6, page 588 of D1 for extraction of penicillin carboxylic acid esters, however, it should be noted the solvent extraction of such carboxylic acid esters is mediated through the use of a phase-transfer catalyst.

Further, even though, D1 mentions a similar solvent extraction process for isolation/purification of cephalosporin compounds (See Section 3.4, page 589-590) it should be noted that like in the case of penicillins mentioned hereinabove the cephalosporin compounds dealt therein are those obtained through fermentation such as Cephalosporin C, Deacetyl Cephalosporin C etc, which, needless to mention, are again un-ionized cephalosporanic acid derivatives i. e. those possessing a free carboxylic acid function at the 4-position of the respective compounds. These free carboxylic acid function at the 4-position of the cephalosporin compounds like the penicillins are capable of forming the alkali metal or organic base salts.

From the foregoing, it would be abundantly evident that this document D1 essentially teaches :

a) extraction/isolation of penicillins or cephalosporins from a fermentation broth taking advantage of the distribution of an un-ionized penicillinic acid/cephalosporanic acid i. e. a penicillin/cephalosporin having a free carboxylic acid at the 3/4-position in an organic solvent or an ionized penicillin/cephalosporin salt, specially alkali metal salts or organic base salts in water depending on their distribution ratio (Section 2.2 and 3.4); and

b) extraction of penicillin carboxylic acid ester derivatives mediated through use of a phase-transfer catalyst (Section 2.6).

As mentioned earlier, the selective distribution ratios of the penicillin/cephalosporin and its salts in the organic solvent and water respectively has not only the advantage of extracting the most optimum quantity of the penicillin/cephalosporin from the broth but also selectively rejecting most of the unwanted impurities, resulting in obtaining the said penicillin/cephalosporin in pure form.

The invention disclosed in the PCT International Application No. PCT IN03/00003 differs from the method(s) described in the document D1 in the following respects:

i) Our invention relates to a highly selective method for purification and isolation of a semi-synthetic cephalosporin antibiotic, viz. cefpodoxime proxetil from a reaction mixture of its manufacture, which is not a fermentation broth, whereas document D1

teaches a method of extraction of a naturally occurring penicillin or cephalosporin compound from a fermentation broth in which it is manufactured;

ii) Document D1 relates to extraction of conventional penicillins and cephalosporins, characterized by the presence of conventional acyl groups at the 6β/7β positions and a free carboxylic acid function at the 3/4- positions, whereas our invention deals with an unconventional cephalosporin antibiotic, characterized by the presence of a methoxymethyl group at the 3α-position; a 2-(2-aminothiazol-4-yl)-2(Z)-methoxyimino-acetamido function at the 7β-position, and a 1-[(isopropoxycarbonyl)oxy]ethyl carboxylic acid ester group at the 4-position of the molecule;

iii) The highly selective method for purification and isolation of cefpodoxime proxetil as per our invention involves the intermediary of an acid addition salt of the compound, comprising formation of its methanesulfonic acid salt, which is selectively partitioned in water, leaving behind all impurities in an organic phase whereas document D1 teaches isolation/purification of a naturally occurring penicillinic acid or cephalosporanic acid derivative from a fermentation broth either in the un-ionized form (as the free 3-carboxylic acid) or in an ionized form through the intermediary of its alkali metal salt or salt with organic bases; and

iv) In the applicants' method the selective partitioning of the methanesulfonate salt of cefpodoxime proxetil in water proceeds without use of a phase-transfer catalyst whereas document D1 teaches partitioning of a penicillin carboxylic acid ester in an organic phase through the use of a phase-transfer catalyst;

In addition,

a) Since cefpodoxime proxetil is characterized by the presence of a 1-[(isopropoxycarbonyl)oxy]ethyl carboxylic acid ester group at the 4-position of the molecule, which is prone to hydrolysis under basic conditions; the presence of 2-(2-aminothiazol-4-yl)-2(Z)-methoxyimino-acetamido function at the 7β-position, the amino function of which is reactive; and the tendency of the molecule to isomerize to the Δ^2-isomer, the impurities formed in a manufacturing process of cefpodoxime proxetil are entirely different from those formed during a fermentive process for manufacture of the penicillin/cephalosporin compounds described in document D1;

b) Removal of all the impurities and moreover, maintaining a diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6 in the final product is requires special and selective purification methods ; and

c) a solution for which cannot be obvious to or anticipated by a person skilled in the art from the teachings of document D1.

Moreover, as mentioned at the outset, there is no connection between the method of document D1 and the method disclosed in PCT International Application No. PCT/IN03/00003, wherein the said document D1 could qualify as prior art for a method for purification of cefpodoxime proxetil.

For ready reference, the distinguishing features of the invention disclosed in the PCT International Application No. PCT/IN03/00003 *vis-à-vis* the methods described in document D1 is summarized in **Chart-I**.

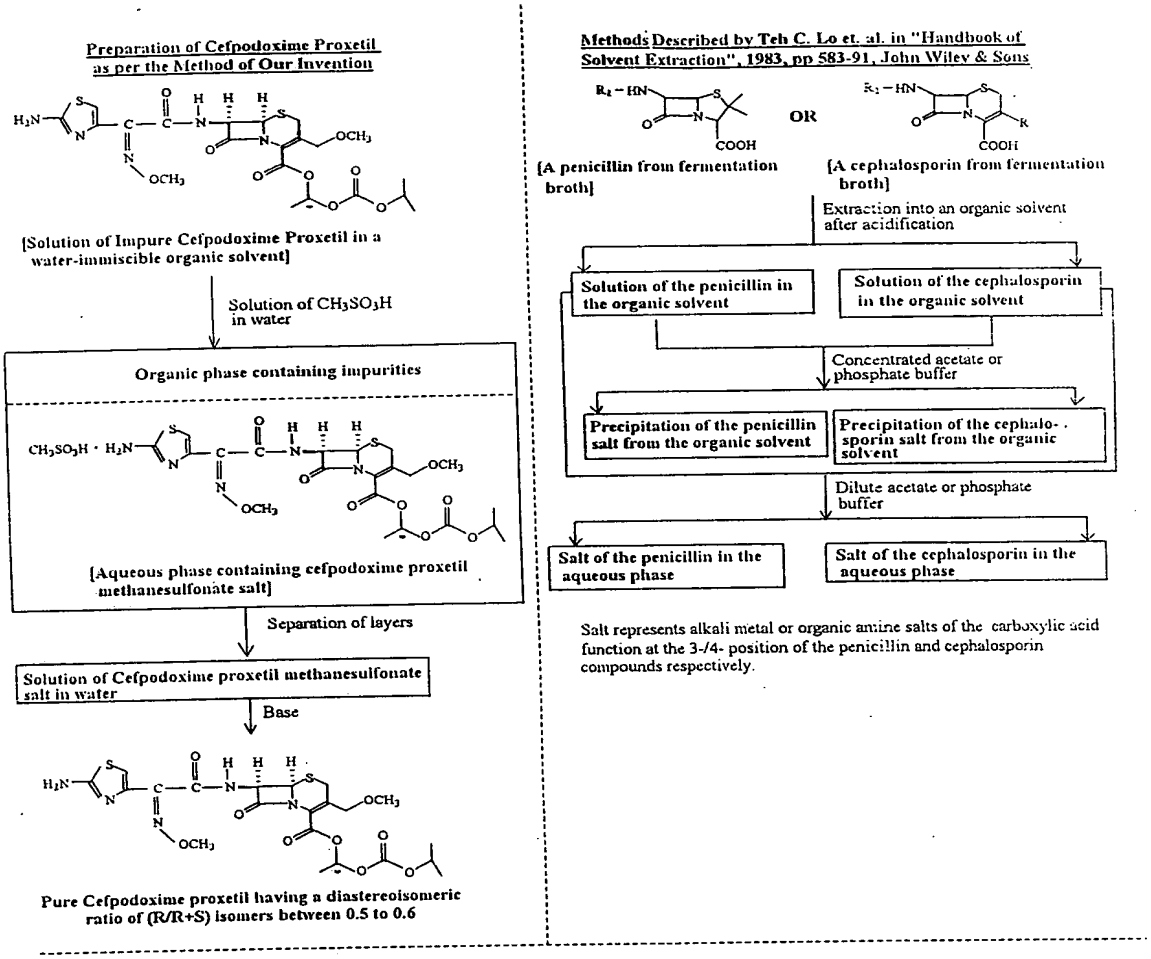


Chart-I: Comparison of the Methods for Preparation of Cefpodoxime proxetil as per Our Invention and the extraction of penicillins and cephalosporins as per the methods described by Teh C. Lo et. al. in "Handbook of Solvent Extraction" 1983, 583-591, John Wiley & Sons

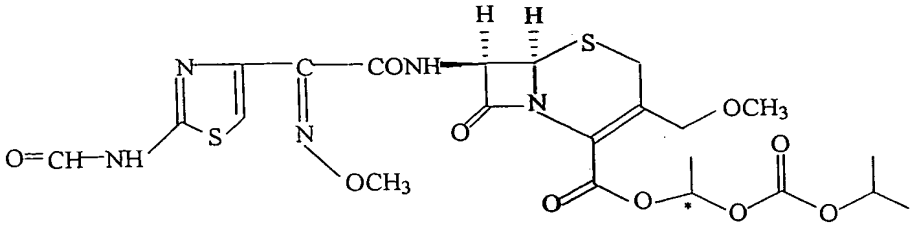
In view of the above, it is respectfully submitted that there in nothing in D1 which would motivate a person skilled in the art towards the present invention.

3B *WO 00/66594*

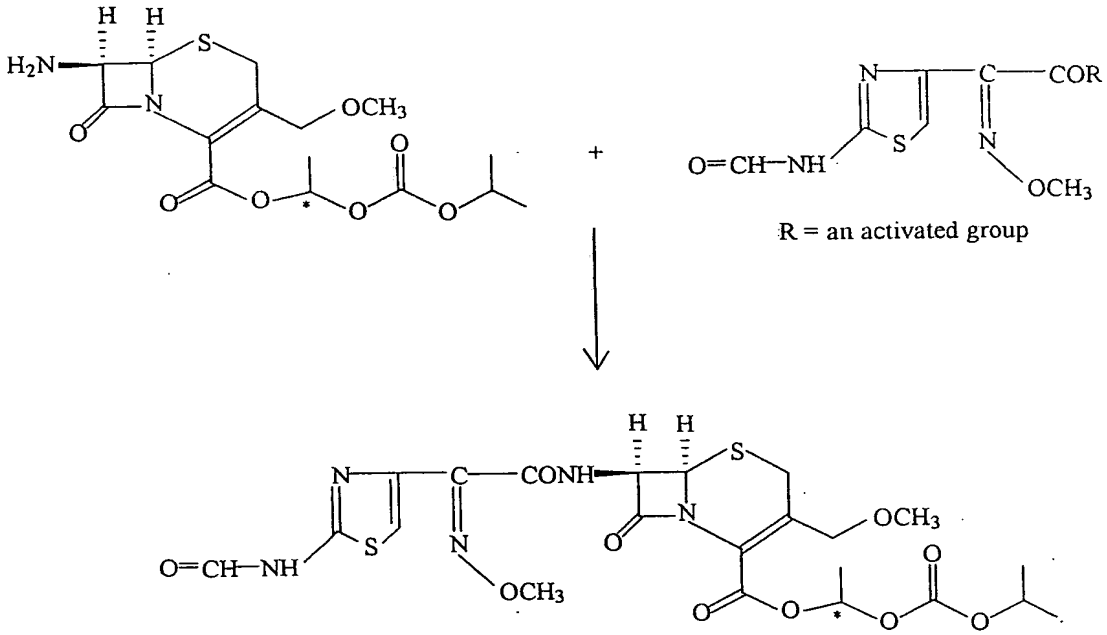
This document also marked "Y" in the International Search Report and in the present context designated as D2 is a patent application by M/S Biochemie G.M.B.H., having an International Filing Date of May 03, 2000 and a Austrian Priority Date of May 05, 1999, both of which are earlier than the filing date (Jan 06, 2003) of the PCT International Application No. PCT/IN03/00003.

As mentioned at the outset, D2 has no connection, whatsoever, with the method of preparation of pure cefpodoxime proxetil, disclosed in the PCT International Application No. PCT/IN03/00003.

This document D2 essentially teaches a method for preparation of cefpodoxime proxetil having a diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6 through the intermediary of a derivative in which the amino group at the 2-position of the 2-(2-aminothiazol-4-yl)-2(Z)-methoxyimino-acetamido addendum at the 7β-position of the molecule is protected as the formyl derivative i. e. via the intermediary of N-formyl cefpodoxime proxetil of the formula shown below.



The document D2 further mentions that in a method for preparation of N-formyl cefpodoxime proxetil comprising acylation of 7-amino-3-methoxymethyl-3-cephem-4-carboxylic acid-(isopropoxycarbonyloxy)ethyl ester with an activated Z-2-(2-formylaminothiazol-4-yl)-2-(methoxyimino) acetic acid (as per the reaction sequence shown below), the object N-formyl cefpodoxime proxetil obtained having a diastereoisomeric ratio of (R/R+S) isomers of 0.40 to below 0.50, which does not conform to the pharmacopoeial specification of 0.5 to 0.6. (See page 1, lines 21-25 and page 2, lines 1-11).



R = an activated group

Further, splitting off the formyl protective group in the N-formyl cefpodoxime proxetil thus obtained was found to give cefpodoxime proxetil having a diastereoisomeric ratio of (R/R+S) isomers outside of 0.5 to 0.6, which again does not conform to the pharmacopoeial specification of 0.5 to 0.6. (See page 2, lines 11-15).

The cited document D2 claims that when the crude or impure N-formyl cefpodoxime proxetil thus obtained is crystallized from an organic solvent selected from a nitrile or a ketone, preferably acetonitrile in presence of water a crystalline N-formyl cefpodoxime

proxetil results, which possesses the desired diastereoisomeric ratio of (R/R−S) isomers = 0.5 to 0.6 and more importantly, when the formyl protective group of the crystalline material thus obtained is split off the cefpodoxime proxetil obtained thereby also is found to possess the desired diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6.

The inventive step residing in document D2, therefore comprises

a) Crystallization of crude N-formyl cefpodoxime proxetil from an organic solvent selected from a nitrile or a ketone, preferably, acetonitrile in presence of water to give a crystalline N-formyl cefpodoxime proxetil, which not only is free of impurities but also possesses the desired diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6; and

b) Splitting of the N-formyl group by treatment with an acid, followed by isolation of pure cefpodoxime proxetil, free of impurities and possessing the desired diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6.

The method of preparation of pure cefpodoxime proxetil disclosed in the PCT International Application No. PCT/IN03/00003 differs from the method disclosed in document D2 in the following respects :

i) The applicants' method does not involve the intermediary of N-formyl cefpodoxime proxetil at any stage of the process;

ii) Unlike the method disclosed in D2, which takes recourse to crystallization of N-formyl cefpodoxime proxetil to adjust the diastereoisomeric ratio of (R/R=S) isomers to the desired level no such adjustment of the diastereoisomeric ratio is required in the applicants' method and cefpodoxime proxetil having the desired diastereoisomeric ratio of (R/R+S) isomers = 0.5 to 0.6 is directly obtained through a simple step of converting impure cefpodoxime proxetil into its methanesulfonate salt, which is selectively partitioned from the impurities in water and the free base i. e., efpodoxime proxetil is regenerated by neutralization of the salt.

With regard to the question of any similarity of the method utilized by us for neutralization of the methanesulfonate salt with a base and the deformylation of N-formyl cefpodoxime proxetil with an acid, followed by treatment of the deformylated compound with a base, as described in Example 5 (page 12) of D2, it might be pointed out that

a) the purpose of treating crystalline N-formyl cefpodoxime proxetil with sulfuric acid in Example 5 of D2 is for splitting off the formyl group to generate the free amino function of the 2-aminothiazole moiety and not to make a salt of cefpodoxime proxetil with sulfuric acid at the 2-position of the 2-(2-aminothiazol-4-yl)-2(Z)-methoxyimino-acetamido addendum at the 7β-position of the molecule and the purpose of adding the reaction mixture containing the cefpodoxime proxetil thus obtained into a dilute solution of aqueous potassium bicarbonate is for precipitation of the product and neutralization of any residual acid present in the product, while

b) the purpose of treating the methanesulfonate salt of cefpodoxime proxetil with a base in a water-miscible or water-immiscible solvent in the applicants' invention is for neutralization of the methanesulfonate salt and precipitation of the free base i. e., cefpodoxime proxetil.

In view of the foregoing, it will be clear that there is no connection between the methods disclosed in document D2 and the method embodied in the PCT International Application No. PCT/IN03/00003 for preparation of cefpodoxime proxetil. Therefore, the applicants respectfully submit that the invention residing in their PCT International Application No. PCT/IN03/00003 cannot be even remotely considered to be obvious or anticipated from the teachings of WO 00/66594.

A comparison of the applicants' method with that disclosed in WO 00/66594 is summarized in **Chart-II** for ready reference.

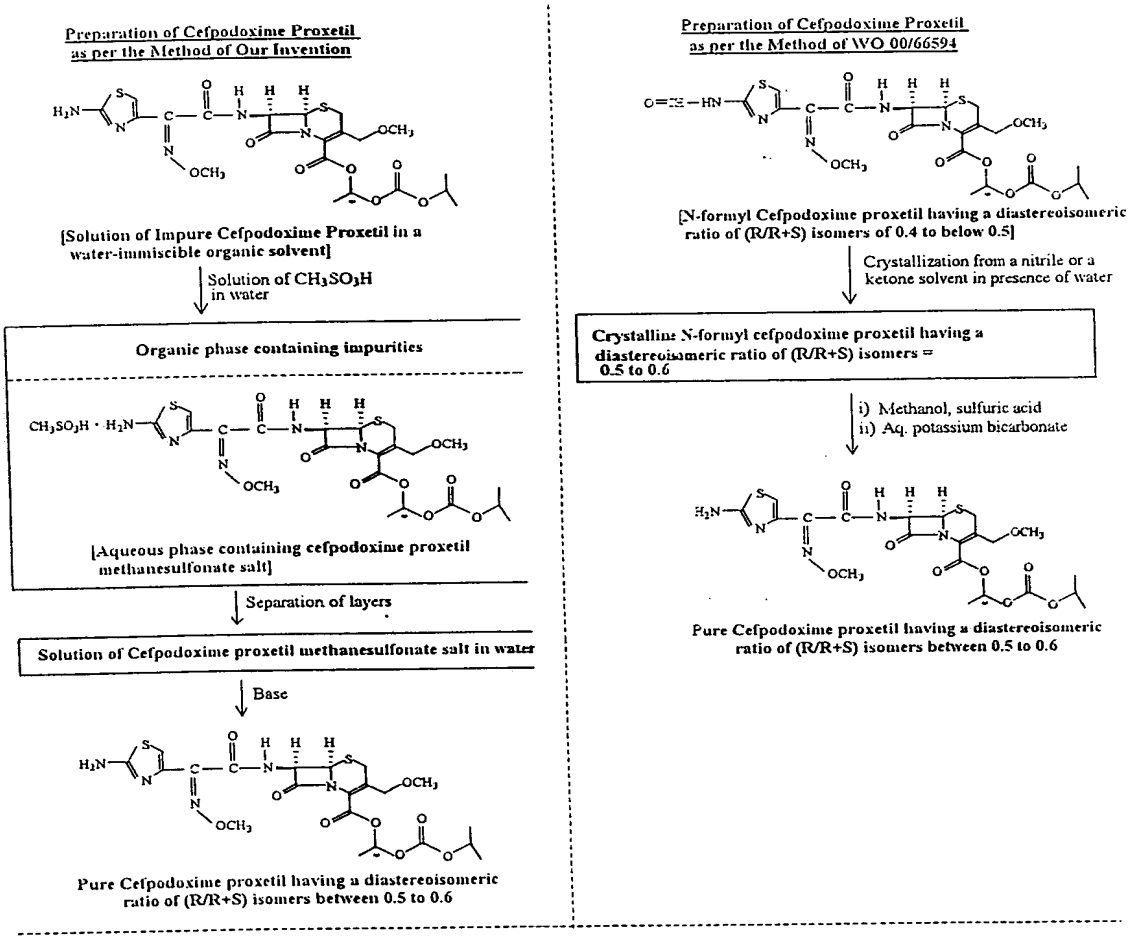


Chart-II : Comparison of the Methods for Preparation of Cefpodoxime proxetil as per Our Invention and as disclosed in WO 00/66594

In view of the above, it is respectfully submitted that the above citation taken alone or in combination with any other document does not render obvious the invention claimed in the PCT International Application No. PCT/IN03/00003.

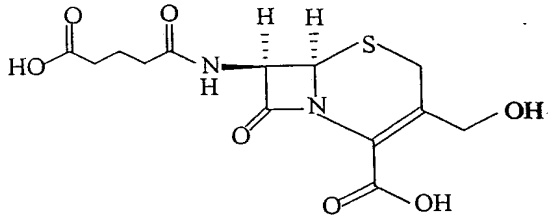
3C *WO 98/04564*

This document also marked "Y" in the International Search Report and in the present context designated as D3 is a patent application by M/S Bristol-Myers Squibb Co. having an International Filing Date of Jul 18, 1997 and a Priority Date of Jul 29, 1996, both of

which are earlier than the filing date (**Jan 06**, 2003) of the PCT International Application No. PCT/IN03/00003.

As mentioned at the outset, D3 has **no** connection, whatsoever, with the method of preparation of pure cefpodoxime proxe**til, dis**closed in the PCT International Application No. PCT/IN03/00003.

This patent application D3 relates to **a process** for obtaining a concentrated aqueous solution (≥ 10% weight/volume) of de**sacetyl**-7-glutaryl ACA (of formula shown below) from a dilute aqueous solution (ferme**ntation** broth) containing the same comprising



i) contacting the said fermentation br**oth with** cyclohexanone at a pH of from about 1.5 to about 3.0 to extract the desacetyl-**7-** glutaryl ACA into the cyclohexanone and separation of the layers thereof; and

ii) contacting the separated cyclohexa**none** phase with water at a pH of from about 5.0 to 7.5 and separating the aqueous phase **containing** the desired concentrated solution of desacetyl-7- glutaryl ACA.

This document D3 while describing the shortcomings associated with the extraction of desacetyl-7- glutaryl ACA from a fermentation broth in the prior art methods states that while it is difficult or impossible to **extract** the product from the fermentation broth by employing common organic solvents, **however**, only the use of cyclohexanone results in optimum extraction of desacetyl-7- **glutaryl** ACA from the broth in a higher concentration.

From the above, it would be apparent that this document D3 specifically teaches extraction of desacetyl-7- glutaryl ACA from a fermentation broth using selectively cyclohexanone as solvent.

Thus, it is respectfully submitted that the applicants' invention relating to a selective method for purification of cefpodoxime proxetil in cannot in any way be connected with the method of extraction of desacetyl-7- glutaryl ACA from a fermentation broth as claimed in WO 98/04564. Accordingly, it is respectfully submitted that the applicants invention covered by their PCT International Application No. PCT/IN03/00003 cannot be construed to be even remotely obvious in view of the method disclosed in WO 98/04564.

4. *SUMMARY*

In summary,

i) The high selectivity exhibited by methanesulfonic acid over other acids in making the salt obtained thereof of cefpodoxime proxetil highly soluble in water, thereby effecting the most optimum separation of impurities in the organic phase, followed by

neutralization of the methanesulfonate salt to give highly pure cefpodoxime proxetil, free of impurities and having a diastereoisomeric ratio of (R/R=S) isomers = 0.5 to 0.6 forms the inventive step of the applicants' invention disclosed in their PCT International Application No. PCT/IN03/00003.

ii) There is no connection between the method disclosed in the applicants' PCT Application No. PCT/IN03/00003 with any of the methods disclosed in documents D1, D2 and D3 cited in the International Search Report and these citations taken individually or in combination cannot render obvious the applicants' invention disclosed ion PCT International Application No. PCT/IN03/00003.

In view of the above, we respectfully request a favourable International Preliminary Examination Report.

Yours Sincerely,

Hari Subramaniam